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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte LUDOVIC CLARION, MARCEL MERSEL, and DIDIER PETITE

Appeal 2019-004144
Application 14/399,336[1]
Technology Center 1600

Before JEFFREY N. FREDMAN, JOHN G. NEW, and DAVID D. COTTA, *Administrative Patent Judges*.

COTTA, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 relating to sterol derivatives for treating transformed astrocyte cells or for treating malignant haemopathies. Spec. 1. The Examiner rejected the claims on appeal as obvious under 35 U.S.C. § 103(a). A hearing was held on April 1, 2020.[2] We reverse.

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[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. According to Appellant, the real party in interest is BETA INNOV. Appeal Br. 1.

[2] A transcript from the hearing has been entered into the record ("Tr.").

STATEMENT OF THE CASE

The Specification discloses that "7β-Hydroxycholesterol (7β-OHCH), a molecule with high anti-cancer potential, shows remarkable cytotoxicity on immortalized (spontaneously transformed) rat astrocyte lines and GBMs (rat line C6) 'in vitro.'" Spec. 4 (internal citations omitted). The Specification also discloses that the esterification of 7β-OHCH at C3-OH by intracellular fatty acids, has been implicated in the toxic effect of 7β-OHCH. *Id.* However, according to the Specification, "the mechanism of action of 7β-OHCH, whether or not esterified at C3-OH, . . . 'in vitro' was far from being elucidated." *Id.*

The Specification discloses:

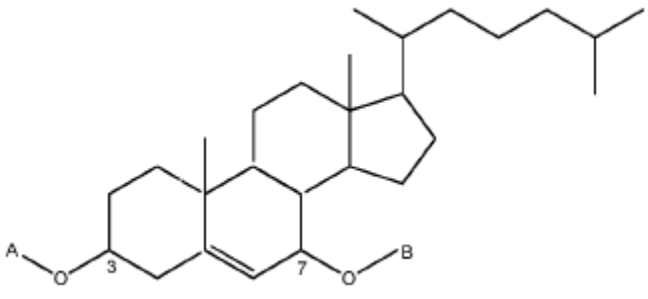
> Surprisingly, it has now been found that the sterol derivatives according to the invention, having a 7beta-hydroxycholesterol basic structure bearing substituents in position 3 and protective groups in position 7, would simultaneously permit inhibition of glycolysis, essential for the energy supply of the high-grade cancerous astrocyte and, at the same time, restore mitochondrial respiration, which is also "lethal" for this cell.

Id. The Specification further discloses that "the sterol derivatives according to the invention also have activity with respect to stem cells, thus permitting total destruction of the glioblastoma cells." *Id.* Based on these properties, the Specification concludes that one can envisage the use of the disclosed sterol derivatives to treat: malignant haemopathies of the myeloid type, neuroblastomas, melanomas, and lymphomas. *Id.* at 5.

Claims 23–26, 28, 29, 31–37, 39–46, 48–50, and 52–62 are on appeal. Claim 23 is representative and reads as follows:

> 23. A compound of formula (I) having a 7beta hydroxycholesterol basic structure

in which



(I)

A represents:

an -$(R_1)_n$- group in which R_1 is an amino acid residue, n = 1 or 2, each R_1 being identical or different, and the N-terminal end of said amino acid is optionally substituted with an arylalkoxycarbonyl group; or

a -C(O) -R_6 group in which R_6 is a saturated heterocycle comprising 5 to 14 members and including 1 or 2 heteroatoms, unsubstituted or substituted with at least one linear or branched C_1-C_6 alkyl

B represents:

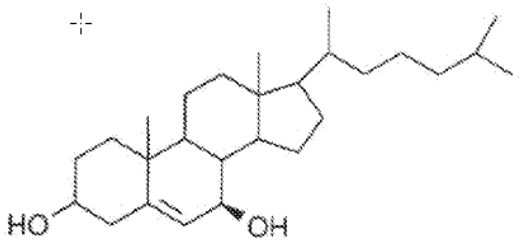
a -C(O)-R_7 group in which R_7 is a C_1-C_{12} alkyl, linear or branched; or R_7 represents OR_8, in which R_8 is a linear or branched, C_1 -C_{12} alkyl.

Appeal Br. 39–40.

The Examiner rejected claims 23–26, 28, 29, 31–37, 39–46, 48–50, and 52–62 under 35 U.S.C. § 103(a) as obvious over the combination of Axelson,[3] Xian,[4] Won Hyun,[5] Reckewell,[6] and Fieser.[7]

REJECTION OF PENDING CLAIMS AS OBVIOUS

In finding the pending claims obvious, the Examiner found that each of Axelson, Won Hyun, and Reckewell disclosed that the below 7β-hydroxycholesterol compound was cytotoxic to various types of tumor cells.



Ans. 3. The Examiner acknowledged that these references did not teach 3,7-diesters of this compound, as recited in the pending claims, but found that Xian disclosed esters of 7β-hydroxycholesterol. *Id.* at 4. The Examiner then concluded that the claims were obvious because "an ester is ordinarily unpatentable over the alcohol from which it is derived" and because "the esters, as exemplified by Xian et al., . . . are well known prodrugs." *Id.* (citing *Ex parte Korten*, 71 USPQ 173 (Bd. App. 1946)).

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[3] Axelson et al., WO 97/45440, published Dec. 4, 1997 ("Axelson").
[4] Xian et al., *Studies on the Synthesis and Antitumor Activities of Oxysterol Derivatives*, Chinese Journal of Medicinal Chemistry (2005) ("Xian").
[5] Won Hyun et al., *Effects of Combinations of 7β-hydroxycholesterol and Anticancer Drugs on Ionizing Radiation on the Proliferation of Cultured Tumor Cells*, 22(2A) Anticancer Research 943–948 (2002).
[6] Reckewell et al., *In Vitro Study of the Cytotoxicity and Selectivity of 7β-hydroxycholesterol*, 37(2) Arzneimittel-Forschung 139–141 (1987) ("Reckewell").
[7] Fieser et al., *"α" – Spinasterol*, 71 Journal of the American Chemical Society 2226–30 (1949) ("Fieser").

Appellant argues that the Examiner did not identify a "suggestion to modify either 7β-hydroxycholesterol of AXELSON, WON, [and] RECKEWELL . . . or any of the esters of XIAN to approach [the] compound of claim 23." Appeal Br. 12. More specifically, Appellant argues that "none of [the cited] references discloses or suggests the structure of the moiety A of claim 23." Reply Br. 2.

As stated in *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992): "[T]he examiner bears the initial burden . . . of presenting a *prima facie* case of unpatentability." Appellant has persuaded us that the Examiner has not carried the burden of establishing that the claimed invention would have been obvious over the cited art.

We recognize that the claimed compounds are esters — or, more specifically, diesters — of the 7β-hydroxycholesterol compound disclosed in Axelson, Won, and Reckewell. We further recognize "an ester is ordinarily unpatentable over the alcohol from which it is derived, since esterification is such a well understood and widely practiced procedure in the chemical art, generally, that the conception of an ester derived from a known alcohol is not inventive, broadly." *Ex Parte Korten*, 71 USPQ 173, *1 (Pat & Tr. Office Bd. App. 1946) (affirming the examiner's determination that a "broadly stated ester of a given alcohol is not patentable over the alcohol itself"). However, this is not a case where Appellant has broadly claimed esters of 7β-hydroxycholesterol. Rather, Appellant has claimed compounds having specific ester moieties. The question before us is thus not, broadly speaking, whether esters of the prior art 7β-hydroxycholesterol compound would have been obvious, but whether a compound having the specific ester moieties recited in claim 23 would have been obvious.

In *Takeda*, the Federal Circuit provided the following guidance on analyzing obviousness based on the structural similarity of a prior art compound to the claimed compound:

> Our case law concerning prima facie obviousness of structurally similar compounds is well-established. We have held that "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness." *Dillon,* 919 F.2d [688,] 692 [(Fed. Cir. 1990)]. In addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of "adequate support in the prior art" for the change in structure. *In re Grabiak,* 769 F.2d 729, 731–32 (Fed. Cir. 1985).
>
> We elaborated on this requirement in the case of *In re Deuel,* 51 F.3d 1552, 1558 (Fed. Cir. 1995), where we stated that "[n]ormally a prima facie case of obviousness is based upon structural similarity, *i.e.,* an established structural relationship between a prior art compound and the claimed compound." That is so because close or established "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds." *Id.* A known compound may suggest its homolog, analog, or isomer because such compounds "often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." *Id.* We clarified, however, ***that in order to find a prima facie case of unpatentability in such instances, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required.*** *Id.* (citing *In re Jones,* 958 F.2d 347 (Fed. Cir. 1992); *Dillon,* 919 F.2d 688; *Grabiak,* 769 F.2d 729; *In re Lalu,* 747 F.2d 703 (Fed. Cir. 1984)).

Takeda Chem. Indus., Ltd. v. Alphapharm Pty. Ltd., 492 F.3d 1350, 1356 (Fed. Cir. 2007) (emphasis added).

Under the framework set forth in *Takeda*, in order to support that it would have been obvious to modify the 7β-hydroxycholesterol compound disclosed in the art to include the ester moieties recited in claim 23 at the 3 and 7 positions, there must have been a reason why the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention." *Id.* (quotation marks and citations omitted). Here, the only explanation offered by the Examiner as to why the ordinary artisan would have modified the prior art 7β-hydroxycholesterol compound to include moiety A at the 3 position and moiety B at the 7 position is to point to the structural similarity between an ester and an alcohol. Accordingly, we find that the Examiner has not carried the burden to establish that the claimed compound would have been obvious over the cited art. As this deficiency is common to the Examiner's rejection of all of the pending claims, we reverse the Examiner's rejection of claims 23–26, 28, 29, 31–37, 39–46, 48–50, and 52–62 under 35 U.S.C. § 103(a) as obvious over the combination of Axelson, Xian, Won Hyun, Reckewell, and Fieser.

CONCLUSION

In summary:

Claims Rejected	35 U.S.C. §	References(s)/ Basis	Affirmed	Reversed
23–26, 28, 29, 31–37, 39–46, 48–50, 52–62	103	Axelson, Xian, Won Hyun, Reckewell, Fieser		23–26, 28, 29, 31–37, 39–46, 48–50, 52–62
Overall Outcome				23–26, 28, 29, 31–37, 39–46, 48–50, 52–62

REVERSED